



Patent Application of  
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for

ANTIFUNGAL BOTANIC EXTRACTS  
AND RELATED COMPOUNDS

**Technical Field**

The invention relates to a new class of general antifungal compounds obtainable from plant species of the pepper, and ginger families, and chemically related species useful in the treatment of fungal disorders.

**Background Art**

There is a wide array of fungi pathogenic to man and animals. The disease they cause are classified into two broad categories; as deep tissue, or systemic mycoses, and superficial mycoses.

Deep tissue, or systemic mycoses including aspergillosis, blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, paracoccidioidomycosis, entomophthoromycosis and candidiasis may involve widespread growth, and dissemination of fungi in internal organs, and tissue. The lungs, brain, bones, spinal fluid, liver, heart, kidneys, other internal organs, and skin being subject to infection that can be life threatening.

Prevalence of deep tissue mycoses is on the rise due to the high susceptibility, and ever growing number of immunocompromised patients. These include cancer, organ transplant patients, and others on immunosuppressant medication, and particularly with patients suffering from immune disorders such as acquired immune deficiency syndrome (AIDS).

Antibiotic drugs such as penicillin, tetracycline, and sulfa ect., though often effective against bacterial infections, are useless against infections caused by fungi. Treatment with a separate group of antifungal, or antimycotic antimicrobial drugs is required.

Antimycotic drugs were first introduced in the 1950's with nystatin (1954), amphotericin B (1958), and griseofulvin (1959). These drugs were originally administered systemically. Tolnaftate was introduced in 1965 as the first effective topical antifungal treatment. Since the 1970's, a number of

"azole" derivative antifungals such as clotrimazole, miconazole, econazole, ketoconazole, and others have made their appearance as antimycotics for both systemic, and topical administration. The more current trend has been toward the development of a "triazole" class of antifungals, including fluconazole, terconazole, and itraconazole ect..

Systemic treatment with antimycotic drugs is prolonged, very expensive, and dangerous, with many adverse effects. Complications arising from therapy can itself be life threatening due to the high toxicity of these drugs. The risk of damage to internal organs, adverse effects on blood composition, and adverse reactions to other medications is a very complex matter that must be carefully monitored by administering physicians. With this, other less severe, yet unpleasant side effects, include nausea, vomiting, headache, dizziness, fever, diarrhea, and many others that contribute to complications, and the misery and ill health of the patient. Other adverse effects, now unknown may yet be discovered.

Amphotericin B, given by injection in the treatment of systemic fungal infection, carries with it the risk of liver and kidney damage, and can also result in blood disorders. It interacts negatively with many cardiac medications, and diuretics, as well as other antibiotics.

Griseofulvin, usually taken orally, for fungal infections of the skin, hair, and nails, has a risk of liver damage. Reduced bone marrow function, with lowered white cell levels is another possible adverse effect of treatment. Drug interactions with anticoagulants, and barbiturates reduce effectiveness, and the risk to pregnancy often forbids treatment.

Ketoconazole, taken orally for systemic fungal infections, also carries the risk of liver damage as a result of treatment. The effectiveness of ketoconazole is diminished by interaction with various antacids, and other gastric medications. Ketoconazole increases the potency of other drugs, and is reduced in potency by some antibiotics.

Miconazole, taken by injection for fungal infection of the lungs, brain, kidney, and lymph nodes, can alter blood chemistry resulting in anemia. Miconazole also interacts negatively with medications for diabetes, epilepsy and anticoagulants. The effectiveness of amphotericin B is reduced by miconazole.

Nystatin, taken orally for candida disorders, is of little use in the treatment of systemic fungal infections. Though having far fewer adverse side

effects than the other antifungal drugs, it is ineffective against most fungal infections except candida, and aspergillus, making it of limited usage.

These adverse effects are particularly devastating to immunocompromised patients, those in most need of treatment. Complications from treatment may well end their life.

Similar problems of low effectiveness, prolonged treatment, and high cost of prior art antifungals affect the treatment of superficial mycoses.

Superficial mycoses, also called dermatophytoses the skin, hair, nails, or mucosal linings are infected with any of three dozen or so different species of yeast and fungi. More specifically, ringworm (tinea) in it's various forms including athlete's foot (tinea pedis), favus, or scalp ringworm (tinea capitis), body ringworm (tinea corporis) jock itch (tinea cruris) etc., and skin, and mucosal candidiasis among others.

The National Health Survey of 1971-1974 projected from its sampling that about one out of every twelve people in the United States had some form of dermatophytosis, with men being four times more likely than women to contract infections.

Surveys of other nations reveal a much higher incidence of superficial mycotic diseases, among the poor, and underdeveloped countries of Africa, Asia, South America, and those areas of the world having tropical climates.

Though not considered life threatening, as some deep tissues disorders can be, the superficial varieties assuredly take a fair toll in misery, inconvenience, and expense.

Certainly anyone with painful cuts on the feet, bald patches on the scalp, unsightly thickening, brittleness, and discoloration of the fingernails, or an unsightly, itchy rash due to a chronic fungal infection may feel they have a serious illness.

Certainly, the economically disadvantaged would consider any disorder that in addition to causing discomfort, could cost them several hundred dollars a year in treatments without cure "serious".

Likewise, those in the livestock industry may think of ringworm as a serious disease when herds are refused because of ringworm infestation. Being highly contagious, this can occur in just a few weeks without remedy.

Prior art treatments for superficial mycoses, in addition to being expensive, require repeated application before improvement can be seen in the

patient. Currently available over the counter treatments, containing clotrimazole, miconazole, tolnaftate, or undecylenic acid, recommend up to sixty applications of the product in order to provide full benefit. More treatments are often required.

~~Even~~ Even prescription topical antifungals, administered by a dermatologist, may require as many as two hundred applications over a period of three months to cure some cases of athlete's foot alone. Nail infections may require eighteen months of multiple, daily treatment to provide cure. In addition to being very expensive and time consuming, applying the medicine repeatedly each day is bothersome. Coupled with the discomfort of the fungal disorder, the expense, and inconvenience associated with the treatment adds further to the misery of the condition.

Regardless of economic impact, even wealthy individuals, with the best health care available suffer with all the others when it comes to the discomfort, and bother of repeated application of medication that is slow acting, and often ineffective at producing cure or relief of symptoms.

The current cost of treating ringworm and other superficial mycoses excludes the economically disadvantaged, who suffer most from the condition, from receiving treatment. Poor sanitation and a lower standard of general health adds to the greater prevalence of ringworm, and other superficial mycoses among the poor, and because it is rarely treated because the effectiveness of treatment does not justify the expense.

In this respect, the current array of prior art antifungal treatments have failed. In addition to the misfortune of not having viable treatment for tens of millions of sufferers of fungal infection, no markets are created, and no products sold, to the advantage of no one. Prior art antifungal treatments keep the price of treatment high, the market volume small, and undiverse, and only bring marginal relief to a relative few of the many suffers.

Cost, and ineffectiveness prohibit use of prior art topical antifungals in the livestock industry, as well. The cost of the medicine, coupled with the labor required for repeated application to livestock, forbids the creation of a significant market for these medicines within the industry.

Livestock infected with ringworm are refused by feed lots. Being highly contagious, ringworm can spread through a herd within a few short weeks, not allowing enough time for treatment and recovery in the weeks prior to going to market, even if the animals are treated.

With the current way of topical antifungals, treating food animals for ringworm is an absurd notion. The cost of applying a medicine, perhaps fifty times, to a single head of livestock could never be justified. For this reason, treatment is withheld, to the disadvantage of both the rancher and the animal, which in addition to suffering discomfort, spreads the disease to other animals, perpetuating the cycle further. In addition to money lost, no viable solution is offered by pharmaceutical manufacturers which would otherwise enjoy a new very large potential market.

Whether or not one feels the economic impact of superficial mycoses, all suffers experience the inconvenience of having to make repeated application of currently available prior art topicals. The necessity of making repeated applications is an indication of weak drug action, the great flaw of prior art antifungal treatments.

Topical treatment of superficial mycoses is much safer than internal treatments. The weak action of prior art topical antifungal medications often necessitates the use of systemic treatments, which are more dangerous, costly, time consuming, and associated with many other unpleasant adverse effects mentioned above.

The focus of the prior art upon the development of azole derivatives will continue to keep the cost high, and the effectiveness of antifungal treatments low to the detriment of patient and healthcare economics. The newer generation triazole derivatives, including fluconazole, terconazole, itraconazole, and others, cost many millions of dollars to develop, and apparently are not that much more effective than the prior generation imidazole derivatives, and certainly are doing nothing to make treatment more affordable, or convenient. Beside this, they have much narrower application than the imidazoles, and are considered auxiliary, and not mainline treatments.

It seems doubtful that the azole groups will produce derivatives of significantly greater effectiveness in the treatment of fungal disorders, than what is currently available with prior art treatments. The need for a safe, effective, and low cost treatments is more urgent than ever.

The high cost, low ineffectiveness, and dangerously high toxicity of prior art medications is not suited to deal with the steadily rising number of cancer, AIDS, and immunosuppressant drug treatment cases reported now, and anticipated for the future.

The importance of having medications that are cost effective as well, is becoming critical to the preservation of our very way of life. Escalating health care costs are the primary contributor to the national debt. The high cost of health care insurance in the United States now exclude 1 in 6 Americans from coverage while consuming a greater share of the household budget with each new year. Money otherwise spent on housing, college, retirement, entertainment, and consumer goods must instead go to cover the cost of health care. In addition to a lower standard of living, this takes capital away from industries that provide employment, and tax revenues that pay the national debt.

Should economic ruin be a necessity of adequate health care? Is trading bodily ills for economic ills the only viable option?

People of developing countries of the world experience near total exclusion of healthcare because of cost.

### **Disclosure of Invention**

Several objects and advantages of my invention include an improved treatment for fungal infections of unparalleled effectiveness. A treatment that saves the lives, and misery of millions of sufferers. A low toxicity treatment for fungal infections. A low cost treatment for fungal infections also affordable to the poor. A treatment for fungal infections of broader commercial feasibility. A treatment that saves billions of dollars annually. A treatment that becomes a model for demonstrated savings in healthcare costs including government sponsored healthcare programs such as Medicare, and Medicaid. A veterinary treatment for fungal infections.

I have discovered that pepper, and chemically related compounds, and species of plants contain active agents of unparalleled effectiveness in the treatment of superficial fungal infections. These agents may be administered in the wide range of commonly used drug vehicles and carriers in the form of a **lotion, drops, tincture, plaster, aerosol**, and other vehicles with a level of effectiveness truly generations ahead of currently available prior art antifungal.

Ringworm in its various forms, including athlete's foot, jock itch, and favus, along with other types of dermatomycoses such as candida, may be completely healed in as few as a single treatment with this medication. Body

and scalp ringworm lesions disappear, usually within the first day after treatment, and require no follow up dosage. Recalcitrant cases of athlete's foot are healed in as few as half a dozen doses of my medicine rather than scores of applications, usually required by prior art antifungal medications that often do not cure.

Currently available prior art over the counter topical treatments for ringworm containing clotrimazole, miconazole, tolnaftate, or undecylenic acid, usually require several weeks of daily multiple treatments before improvement can be observed in the condition. In addition to the considerable expense of having to buy several containers of the medication, the time, and inconvenience involved in making repeated applications with meager results adds further to the misery and discomfort of the disease. Even mild to moderate cases of tinea can easily require more than sixty applications of these products before the condition improves. The weak therapeutic action of these prior art, over the counter treatments is often insufficient to produce adequate results. Often, the disorder must be treated by a physician, using prescription topical, and systemic antifungals taken internally.

Prescription treatment with antifungal medications is the most expensive of all treatments. Beside the cost of having an attending dermatologist, the medications themselves are more expensive than the over the counter varieties. This type of treatment, being the best the prior art has to offer, still may require several months of multiple daily doses of the antifungal medication to cure some kinds of ringworm. Treatment for athlete's foot may require up to three months of multiple daily doses of the medicine before the condition can be cured. Ringworm infections of the toe nail can take up to eighteen months to heal. So adding the expense of visits to a dermatologist, time lost from work or leisure, the time and inconvenience of applying the medicine, the cost of the medicine, and the ongoing discomfort of the disorder, all have an economic impact that is quite considerable, in addition to the discomfort of both the disease and the side effects of treatment.

With my treatment, systemic treatment of superficial disorders is likely a thing of the past.

The high effectiveness of pepper appears to be due to multiple therapeutic actions in addition to direct antifungal action. Case observations suggest general healing, keratolytic, immunostimulation and modulation, adjuvant, drug delivery, and prophylactic properties beyond direct fungicidal. In

*vitro* antifungal screens prove proportionally increased potency against terminal drug resistant fungi strains.

It appears that the high nutrient concentration found in pepper including vitamins, minerals, carotenoids, lipids, and others assist the above therapeutic effects addition to the pungent compounds. Pepper compounds are safe, and have been in widespread use as food for thousands of years and do not induce illness as do prior art antifungals.

As a generally recognized as safe (GRAS) listed nutrient food compound, pepper medications are ideal for livestock use. Systemic treatments, and topical medications to control ringworm, candida, and other disorders can be developed. Pepper derivatives may be added to feed to prevent systemic disease as well.

The veterinary market for treatment of mycoses can be greatly broadened given the high effectiveness, low toxicity, and very low cost of my medication. Dermatophyte infections such as ringworm need no longer prevent sale of livestock as before.

Prior art topical antifungals have prevented the formation of a market for the treatment of livestock superficial mycoses To treat food animals such as cattle, with any of the prior art topical antifungals before market is an absurd notion. The cost of medicine, its very slow action, coupled with the very considerable amount of labor required to repeatedly administer the medicine, can not be justified economically. For this reason, no significant market exists within the industry for such products.

With the treatment of the current invention, however, the scope of product possibilities is enlarged by making treatment of these disorders economically feasible.

The many therapeutic properties, and beneficial components found in pepper provide the ideal profile for a systemic treatment for the more serious, and often life threatening deep tissue, and systemic fungal disorders.

Systemic treatment with antifungal drugs, such as amphotericin B, clotrimazole, griseofulvin, ketoconazole, miconazole, nystatin and others, in addition to being expensive and time consuming, have many bad side effects that can further endanger the health of the patient. These drugs, taken internally, carry the risk of damage to liver and other internal organs, and adverse effects upon blood chemistry. Patients receiving such treatments must be monitored for changes in blood and organ function, as a safeguard against



serious damage that can result from treatment. Prior art systemic antifungals also interact adversely with a large number of other medications, another area that requires close attention by the attending physician. Beside this, other adverse effects include nausea, vomiting, diarrhea, fever, headache, anemia, and other unpleasant symptoms that accompany the discomfort of the disease.

The high cost, low ineffectiveness, and dangerously high toxicity of prior art medications is not suited to deal with the steadily rising number of cancer, AIDS, and immunosuppressant drug treatment cases reported now, and anticipated for the future.

Pepper compounds are an important research tool in the war against the increased incidence of life threatening deep tissue, and sytemic fungal disorders.

The impact of commercial implementation of this topical antifungal treatment alone, is to make affordable to even the poorest people of developing countries a certain cure for even the most severe cases of superficial mycoses who are now excluded from care because of the high cost, and low effectiveness of prior art antifungals.

A treatment that cures completely in much less time, in a much safer way, without the need of an attending physician, and for less than one penny on the dollar for what is required of prior art treatments in will bring relief to many hundreds of millions of sufferers, rich and poor alike while expand the consumer demand base for products accordingly.

Full scale implementation of these medications will save in excess of \$20 billion dollars in Gross National Product in the treatment of superficial disorders in the U.S. alone not to mention the world.

This enhanced level of safety, effectiveness, and dramatic cost savings of these medications should serve as a model to government healthcare programs such as Medicaid, and Medicare save billions of dollars in medical expenditures while providing the best care for recipients.

Now and finally, an antifungal treatment exists that can save our nation, and many nations of the world millions of dollars each day in medical costs, and lost productivity, provide highly lucrative products for commercial exploitation, provides an important research tool in the treatment of life threatening illness, and bring speedy relief to hundreds of millions of suffers of fungal disorders, and perhaps even save lives; man and animal alike.

### **Brief Description of the Drawings**

Fig. 1 is a molecular diagram of phenol.

Fig. 2 - 13 show molecular diagrams of compounds of the current invention.

Fig. 2 is a molecular diagram of ortho-methoxyphenol.

Fig. 3 is a molecular diagram of vanillyl.

Fig. 4 is a molecular diagram of 3-methoxy-4-hydroxybenzylamine. Fig. 5 is a molecular diagram of vanillylamide.

Fig. 6 is a molecular diagram of the capsaicinoids.

Fig. 7 is a molecular diagram of piperidine.

Fig. 8 is a molecular diagram of the pungent alkaloid principals of pepper.

Fig. 9 is a molecular diagram of eugenol.

Fig. 10 is a molecular diagram of curcumin.

Fig. 11 is a molecular diagram of gingerol.

Fig. 12 is a molecular diagram of resiniferatoxin.

Fig. 13 is a molecular diagram of tinyatoxin.

### **Best Modes for Carrying out the Invention**

A medicinal preparation of pepper, and its active constituents may be administered in a wide range of conventional drug vehicles and carriers. Capsicum, and black pepper are available commercially as oleoresin, in a wide range of concentrations, and pungencies, and may be used in place of the plant product described below.

The preparations described below are made from a moderate pungency commercial grade of ground cayenne pepper (*Capsicum frutescens*), or black pepper (*Piper nigrum*), as an indicator of approximate concentration within each carrier. Their equivalents may be estimated, and prepared from commercially available oleoresin, or from any of the pungent principals, some of which are also available commercially in pure natural, or synthetic form.

The term "pepper", or "pepper compounds" are used somewhat generically to be inclusive of related botanicals of the Zingiberaceae family including ginger (*Zingiber officinale*), turmeric (*Curcuma longa*), cardamon (*Elettaria cardamomum*), Melegueta pepper (*Aframomum melegueta*), members of the Euphorbia genus including *Euphorbia resinifera*, poinsettia (*Euphorbia*

*pulcherrima*), clove (*Eugenia aromatica*), allspice (*Pimenta officinalis*) and others such as vanilla having similar constituents may be prepared in the same way as pepper by following the general procedures outlined below in the capsicum pepper illustration below. Included among this list of botanicals is of course the other members of the Solanaceae pepper family including members of the *Capsicum* genus with the *annuum*, *baccatum*, and *longum* species.

Among the Piperaceae family, species of the *Peperoma*, and *Piper* genus which include the *retrofractum*, *nigrum*, and *longum* species. Other species of plants having similar chemistry may also be used in place of the above.

Variations in performance of each preparation will vary with type, and concentration of extract, carrier, and solvent used in relation to pathogenic organism involved. The scientific literature may be consulted for more detailed investigations as to chemical properties, solubility, separation, and quantitation of constituent compounds.

For purposes of research, or the treatment of disease, the individual compounds responsible for the pungent quality of red peppers, and other capsicums may be obtained directly from ground red pepper, according to procedures described in the article "Separation and Quantitation of Red Pepper Major Heat Principals by Reverse Phase High-Pressure Liquid Chromatography" by Patrick Hoffman et. al., in the Journal of Agricultural Food Chemistry 1983, Vol. 31, pages 1326 - 1330. Though several related capsaicinoids have been identified in trace amounts, the major capsaicinoids (fig. 6) include:

Capsaicin.  $C_{18}H_{27}NO_3$

N-[(4-hydroxy-3-methoxyphenyl)methyl]8-methyl-6-nonenamide).

Dihydrocapsaicin.  $C_{18}H_{29}NO_3$

(N-[(4-hydroxy-3-methoxyphenyl)methyl]-8methylnonanamide). Norcapsaicin.

$C_{17}H_{25}NO_3$

(N-[(4-hydroxy-3-methoxyphenyl)methyl]7-methyl-5octenamide).

Nordihydrocapsaicin.  $C_{17}H_{27}NO_3$

(N-[(4-hydroxy-3-methoxyphenyl)methyl]-7-methyloctanamide.

Homocapsaicin.  $C_{19}H_{29}NO_3$

(N-[(4-hydroxy-3-methoxyphenyl)methyl]-9-methyl-7decenamide).

Homodihydrocapsaicin.  $C_{19}H_{31}NO_3$

N-[(4-hydroxy-3-methoxyphenyl)methyl]-9methyldecanamide).

N-vanillyl-n-nonamide.  $C_{17}H_{27}NO_3$

(N-[(4-hydroxy-3-methoxyphenyl)methyl]-n-nonamide).

Nonanoic acid vanillylamide.  $C_{17}H_{29}NO_3$

Decanoic acid vanillylamide.  $C_{18}H_{31}NO_3$

Other capsaicinoids, not listed here, are identified in research literature as trace elements within capsicum, and may be used in medicinal preparations as well, along with other analogous compounds.

Capsaicinoids are generally classified as acid amide derivatives of Phenol (fig. 1). The characteristic pungent, irritating sensory effects of these compounds are typical of acid amides, whether derived from phenol, or piperidine (fig. 7).

Phenol (fig. 1), though lacking pungent flavor, is highly corrosive, caustic, and toxic, deriving many of its properties from its basic benzene structure. While this gives phenol certain antimicrobial properties, it is generally considered to be unsuitable for therapeutic use in man, and animals, due to its and irritating effects on tissue.

With the addition of a methoxy group ( $OCH_3$ ) to phenol, methoxyphenol is formed. In the ortho position, we have ortho-methoxyphenol (fig. 2), also known as guaiacum, an extract obtainable from trees of the *Guaiacum* genus. The effect of this methoxy group in part is an increase in aromacy, and a decrease in toxicity, and caustic properties otherwise existing in phenol, yet without apparent decrease in antimicrobial properties. The attachment of hydrocarbon groups to the ring structure, to form higher analogues apparently increases the antimicrobial properties of methoxyphenol, and phenol. It is presumed that the meta, or para isomers of methoxyphenol have similar properties to the ortho, in like manner to the similarities between the phenol isomers.

The addition of the methylene group ( $CH_2$ ) in the para position to ortho-methoxyphenol produces vanillyl (fig. 3). Like phenol, and methoxyphenol, it is presumed that changing the position of the methylene group to form other vanillyl isomers will produce compounds of similar, although not exact properties to that of vanillyl.

The vanillyl structure on which the capsaicinoids are constructed is also typical of the pungent principals found in ginger (*Zingiberaceae*) species of plants.

Collectively known as gingerol (fig. 11): shogaol, paradol, zingerone, gingerol and other analogs, have a different side chain than the

capsaicinoids, and lacking an ammonia ( $\text{NH}_n$ ) group, are neither amines, or amides like the capsaicinoids or piperidine series. Hydrolysis of gingerols yield vanillyl, and a fatty acid side chain, both of which demonstrate like therapeutic properties to the capsaicinoid hydrolytes.

Also members of the ginger, or Zingiberaceae family, turmeric (*Curcuma longa* L.) contains the compound curcumin (fig. 10), actually a vanillal derivative differing from vanillyl by one hydrogen (H) atom having an (CH) substituent, rather than a methylene ( $\text{CH}_2$ ) in the para position. This analog differs further with a side chain unique from the others. Cardamon, allspice, clove, black pepper, and many others contain eugenol, another vanillyl analog with yet another hydrocarbon side chain.

Other botanical sources of vanillyl analogs include gum euphorbium, and extract of certain species of the *Euphorbia* genus, which contain the capsaicin analog resiniferatoxin (fig. 12), along with its analog tinyatoxin (fig. 13) and others.

Replacement of one of the hydrogen (H) atoms of ammonia ( $\text{NH}_3$ ), with vanillyl, and the replacement of the other hydrogen (H) atom with an organic hydrocarbon group produces vanillylamide (fig. 5). In the case of the capsaicinoids (fig. 6), or capsaicin analogs for example, this organic hydrocarbon group is a chain acid ( $\text{R}'$ ), varying from about 8, to 14 carbon atoms, depending upon the particular capsaicinoid. These side chains, both saturated, and unsaturated (including add to the pungency of capsicums, and themselves possess antimicrobial properties of their own, without apparently contributing corrosiveness, or toxicity to vanillylamide.

Hydrolysis of capsaicinoids yield active agents as well. The splitting off of the side acid chain, and it's replacement with a hydrogen (H) atom yields the primary amine vanillylamine, or 3-methoxy-4-hydroxybenzylamine (fig. 4) from vanillylamide (fig. 5), in the case of all capsaicinoids. Conversely, the side acid chain, receiving a hydroxy (OH) group, is converted to a fatty acid, and yields a different hydrolyte for each individual capsaicinoid. In the case of capsaicin (fig. 6), hydrolysis of the side acid chain  $\text{R}'$  (fig. 6)  $\text{CO}-(\text{CH}_2)_4-\text{CH}=\text{CH}-(\text{CH}_3)_2$  yields iso-decylenic acid  $\text{COOH}-(\text{CH}_2)_4-\text{CH}=\text{CH}-\text{CH}-(\text{CH}_3)_2$ .

The piperidine series (fig. 7 & 8)), represent a group of analogous alkaloid compounds from which most of the pungent principals found within plants of the Piperaceae family, of which black pepper (*Piper nigrum*) is a

member, are found. Also classified as acid amides, the piperidine series, like the capsaicinoids found in capsicum species, are primarily responsible for the characteristic sharp, pungent taste of black pepper.

The piperidine ring (fig. 7) structure is diverse from that of phenol (fig. 1). Though also a six membered, ~~carbocyclic compound~~, the piperidine series instead contain one nitrogen (N) hetero atom within the ring. Piperidine is heteroparaffinic, and contains no double bonds. The hetero nitrogen atom within the ring is a contributor to the pungency of these compounds. The attachment of a hydrogen (H) atom to the hetero nitrogen atom within the ring forms the amine structure. Attachment of a hydrocarbon group, in the form of a side acid chain (R" fig. 8) attached to a benzene structure establishes the acid amide structure. These compounds include; piperine  $C_{17}H_{19}NO_3$  (fig. 8), chavicine  $C_{17}H_{19}NO_3$ , piperettine  $C_{19}H_{21}O_3N$ , piperidine  $(CH_2)_5H$ , piperyline, piperolein A, piperolein B, piperanine, and others.

Hydrolysis of the piperidine series, like the capsaicinoids, yield active, pungent compounds. Chavicine, for example is hydrolysed to piperidine, which receives an additional hydrogen (H) atom to form a primary amine, and chavicic acid, which receives the hydroxy (OH) group to form the fatty acid.

Hydrolysis of these capsaicinoid, and piperidine acid amides, as well as the other listed compounds may be accomplished with chemical catalysts, or by boiling a liquid preparation in water. Hydrolysis does not appear to diminish pungency, and in some applications appears to enhance both pungency, and therapeutic action.

The carbonyl group ( $C=O$ ) side chain substituent, common to all the above compounds (except eugenol) is also believed to be a contributor to antifungal activity.

Other active agents found within capsicum include citric acid, vitamins A, B1, B2, C, and E, iron, potassium and niacin in significant quantities, along with other lipids, and carotenoids including capsanthin, capsorubin, and others. Vitamin C concentrations of 100 milligrams per ounce, are the highest of any natural food compound. Vitamin A content is also high, with 6170 I.U. per ounce.

An **infusion** of pepper may be prepared by soaking approximately 4 cm<sup>3</sup> (1/4 teaspoon) of commercially available ground red, or

black pepper, to one liter (1 quart) of water of sensibly comfortable temperature. Set at least ten minutes before use for best results. Strain plant residue before use if desired.

A more potent **tea** uses about 16 cm<sup>3</sup> (1 teaspoon) of ground pepper for each liter (quart) of sensibly comfortable water. ~~Tea may also be prepared from boiling water, or itself be boiled in water before use.~~ Boiling pepper in water assures complete hydrolysis of the pungent principals, which are also active agents.

A **tincture** may be prepared by soaking ground red, or black pepper in a solution containing approximately 60% ethanol, and 40% water. Pure ethanol, and other solvents such as acetone, chloroform, vinegar (acetic acid), and others may also be used. The fluid volume of the solution may be about three, or four times that of the dry volume of the ground pepper. The mixture should be agitated, at least occasionally, over a period of at least two hours, with maximum extraction being obtained after about six hours. Allowing the mixture to sit over night produces excellent results. Strain off the residual ground pepper.

A preparation of pepper **drops** may be obtained by reducing **tincture** through heat, or passive evaporation. **Drops** made by this method are similar in purity to some grades of commercially available oleoresin.

A **plaster, or poultice** may be prepared by mixing ground pepper with water, until it has a paste-like consistency that will assure good adherence to the skin, or cloth to which it is applied.

A **lotion, cream, or shampoo** may be obtained by adding to any commercially available shampoo, cream, or lotion, a portion of **drops, or tincture** equal to approximately 25% of the volume of lotion, cream, or shampoo carrier.

A **douche** is prepared from **infusion, or tea** that is strained of the plant residue material before use.

A **suppository** is made from **drops** in cocoa butter, or gelatin in the same strength as **douche, or lotion**.

An **injection** is prepared from a purified version of **infusion, tea, drops, etc.**, administered intravenously, in tissue, or mixed with, and injected into the spinal fluid.

A **powder** is pepper in ground form, or extracts mixed, and/or bound within a binding powder carrier such as talc.

A pepper **impregnated fabric** include clothing, and shoe liners made from capsicum wool, or any other pepper compound as a safeguard against harboring these pathogens within one's clothing. For individuals who, for example, have a natural proclivity for contracting athlete's foot, socks, or shoes with liners impregnated with pepper may be worn to prevent contamination leading to infection. The same applies to undergarments, and athletic wear, or anything that has contact with the skin, and is a potential contagion of infection.

Treatment recommendations given below are general guidelines and may be altered to suit specific conditions. If one recommended concentration appears unsuitable, the next graduation should be used.

Consideration as to the degree of tissue damage, patient sensitivity to the medication, and certainly how anxious the patient is to be rid of the disorder. In most, if not all dermatophyte infections, should see results not within the first few weeks of daily treatment.

In the lower concentrations, an **infusion** may be used in the treatment of milder microbial infections including dermatophyte infections, particularly when tissue damage is minimal.

**Infusion** works well as a scalp rinse, a bath for the feet, and skin, and as a **douche** in the treatment of candida, and other vaginal disorders. **Infusion** is also recommended if patient sensitivity to the higher concentrations becomes significant.

In higher concentrations, a **tincture**, a **powder**, a **poultice**, and a preparation of **drops** are recommended in the treatment of severe dermatophytosis. High concentrates, such as these, are preferred where tissue damage is significant, and where infection sites are causing considerable discomfort for the patient. **Drops** for example, work well for topical treatment of nail infections, ringworm lesions, and infected hair. These high concentrates generally produce cure after the first dose when treating skin lesions, and have a prophylactic action of greatest duration, lasting up to about five days after application. As it is usually necessary to induce substantial healing of the skin as a measure against recontamination, and reinfection of dermatophytes, the higher concentrates appear to be most effective as prophylactics.

A **tea** represents a moderate concentration of pepper compounds. It may be used in the same manner as **infusion**, or in the treatment of more severe cases of dermatophytosis. **Tea** should be used if



infusion fails to bring immediate relief of secondary symptoms, such as itching in athlete's foot, candida, or jock itch, within one hour of the first treatment.

**Tea** may also be used in place of the higher concentration carriers, such as **drops** or **tincture**. It is often equally effective in curing severe cases of dermatophytosis, in which there is significant tissue damage, as the high concentrates. In this case, **tea** is preferred over the high concentrates, particularly if the patient sensitivity to the medication is causing significant discomfort.

**Tea** is also suitable as a gargle, or mouth rinse for thrush, or other fungal infections of the throat, and oral cavity.

For an **injection** of pepper compounds in deep tissue, spinal fluid, or intravenously, milder concentrations, such as **infusion** are recommended for initial treatment. While **injection** of pepper extracts such as capsaicin have been administered safely in animal testing of analgesics, it is not known at this writing if treating humans by injection has been attempted.

A **lotion, or shampoo** may be prepared with any commonly available lotion, or shampoo, and applied to infected areas in its intended manner. Other therapeutic agents, in addition to pepper extracts, may be added to **shampoo and lotion**. If irritation is a concern, a topical anesthetic, such as lidocaine, or benzocaine may be added to **lotion** to reduce severity. If skin is very dry, emollients may also be added to **lotion**.

A pepper **aerosol** may be inhaled in the treatment of throat, and respiratory infections. In this administration, **aerosol** should be derived from a lower concentration such as **infusion**, as pepper is extremely irritating to the nose, throat, lungs, and eyes, especially when airborne. This is especially true of capsicum **aerosol**. For this reason, **aerosol** is somewhat limited in its medicinal application.

The irritating effects of pepper **aerosol**, and particularly capsicum, is greater when distributed within an etheric **tincture** solution, such as alcohol, ether, chloroform, or acetone. Once airborne, even minute concentrations have a tear gas, or mace like effect on the eyes, and respiratory system.

Pepper **powder** is also very irritating when airborne, and like **aerosol**, has a more limited medical application than the other carriers. If used as a foot **powder** for example, it is best to fix the pepper compounds within a powder binder such as talc, to prevent, or lessen escape of airborne particulate.

Below are theories as to the therapeutic actions of pepper compounds based largely on observation, and set forth to further explain the operation of the current invention, and to give direction to areas warranting further research

~~The irritating nature of the purgent compounds are instrumental~~ in precipitating a rapid inflammatory response in the area of administration. In sufficient concentrations, this is observed when applied to skin in the treatment of tinea. The area of treatment often turns red, or pink, and feels warm or hot. Burning, or warm tingling is sometimes reported by patients after topical administration of pepper extracts, usually the result of too high a dosage. Though this burning sensation can become quite intense, it does not usually last beyond the first five or ten minutes after treatment. The burning subsides into a warm, tingling sensation that is no longer uncomfortable to patients. The induction of inflammation to the point of pain is accidental, and not necessary for cure. Inflammatory responses associated with even slight warmth and redness are likely adequate to provide sufficient therapeutic action.

Pepper also appears to act as an immunostimulant, by precipitating leukocytes, and other mononuclear cells, along with a variety of antifungal compounds from the blood, and surrounding tissue, to the area of infection. Though done primarily through inducing inflammation, pain and discomfort are not required in order to receive the full therapeutic benefit. Pepper compounds are also believed to aid in the delivery of these antifungal immune responses of the body, and increase their potency in addition to its own antifungal actions.

The therapeutic value of inflammation, is the stimulation of the body's own immune response in the area of infection. This precipitates a varied array of fungistatic serums, including leukocytes, and other mononuclear cells in the area of infection. These fungistatic serums inhibit the growth of pathogenic fungi.

Inflammation also increases the rate of skin shedding, which combats penetration of the fungus, or other organism into the skin. In this mode of action, the microbe is essentially "cast off" with the diseased tissue. Perhaps for this reason, those varieties of dermatophytosis that are accompanied by inflammation often eventually heal on their own. The noninflammatory varieties such as dry athlete's foot, however become chronic,

and are very difficult to heal. The lack of participation of the immune responses of the host prevents healing, and cure.

It is further possible that pepper compounds act as an adjuvant to these fungistatic serums, by facilitating delivery through blood vessel, skin, and fungal cell membrane pathways. Being composed primarily of lipids, capsicum, for example, may increase the permeability of the cellular membrane of both host, and fungi. In addition to aiding delivery of antifungal serum, the increase in cell membrane permeability may facilitate the delivery of undecylenic acid, another antifungal compound found in sweat, into the fungi. With the aid of increased permeability provided by pepper compounds, antifungal compounds which are normally fungistatic, become fungicidal.

Apart from host response possibilities, the direct antimicrobial properties of pepper and another of the notably pungent botanicals ginger are observed *in vitro*, in addition to those observed in the actual treatment of disease.

A series of *in vitro* tests are conducted on 3 **tincture** samples prepared from the ground spice of cayenne pepper (Sample A), black pepper (Sample B), and ginger (Sample C). Each spice is measured, and mixed with pure ethanol in an amount three times the measured volume.

The mixtures are stored for 18 hours at room temperature (22°C), and agitated on 5 separate occasions over the period. The mixtures are then strained of residue, and submitted for testing. Also included is Sample F; a **tincture** prepared with commercially pure capsaicin (8-methyl-N-vanillyl-6-nonenamide) at a concentration of 25mg. /ml. pure ethanol.

Initial *in vitro* tests performed by a medical university laboratory report that none of the Samples A, B, C, or F show antimicrobial activity against *Candida albicans*, or *Neurospora crassa* on a solid medium, carrot juice agar (pH 6) screening.

A liquid assay *in vitro* screen performed by a major U.S. pharmaceutical company however, reveals activity against all 11 strains of pathogenic fungi tested, including 7 strains of *Candida*! These pathogenic strains are responsible for deep tissue mycotic infection, although the *Candida* strains also cause superficial mycotic infections of the skin, and mucosa as well.

At first glance, a general hierarchy of activity relative to the degree of pungency among the botanical Samples A, B. & C is evident, with cayenne

pepper being most pungent, followed by black pepper, and then ginger. Though exceptions are evident in the tests, degree of pungency is an accurate general "rule of thumb" with regard to evaluating the relative effectiveness. This observation however, for reasons set forth below, should not be interpreted as an indication that therapeutic effects are determined solely by the degree, and quantity of pungent principals present, though it is a factor. This will be further addressed below.

Perhaps most intriguing of the test results below is that Samples A, B, C, & F of the current invention show greatest activity against those fungal strains most resistant to the drug standard Amphotericin B. In particular, *C. albicans* ATCC 38247, *C. kefyr* ATCC 28838, and *T. glabrata* ATCC 15545 show particular sensitivity to Samples A, B, C, & F in this screen. These strains, being most resistant to standard drug therapies, pose the greatest potential for causing life threatening illnesses. The necessity of prolonged treatment with high dosages of highly toxic antifungal drugs required to treat these diseases is often itself life threatening to the patient.

Another important feature of these test findings is evidence of the presence of multiple antimicrobial compounds within the Samples. In comparing Samples A & F for example, it is apparent that the antimicrobial action of cayenne pepper (Sample A) cannot be wholly attributed to the presence of capsaicin alone in the ground spice.

A review of the aforementioned article "Separation and Quantitation of Red Pepper Major Heat Principals by Reverse Phase High Pressure Liquid Chromatograph" indicates by rigorous testing a total "capsaicinoid" content not exceeding about 1.9 mg./gram in common red pepper. Sample A being diluted 3 times with ethanol would fix its maximum capsaicinoid content at perhaps .063%, or about 630 ug. /ml.. Capsaicin accounting for about half of the total capsaicinoid content of common red pepper, would fix the capsaicin content of Sample A at about .032%, or about 320ug/ml.. This diluted 256 times shows Sample A as having activity against *C. albicans* ATCC 38247 at a capsaicin concentration of less than 1.25 ug. /ml., and total capsaicinoid content of less than 2.5 ug./ml against which Amphotericin B requires a concentration of 25 ug/ml. Additionally, capsaicin though the most toxic compound found in any significant amount in capsicum peppers, is much less toxic than Amphotericin B.

In comparison, Sample F has a concentration of pure capsaicin at 25 mg. /ml. - about 40 times the total capsaicinoid content of Sample A, yet is still short of the Sample A performance across the board. This can only mean the presence of another antifungal compound, and/or a synergistic relationship between the mix of capsaicinoids and other compounds within the botanical that account for the total antimicrobial effect. It may also suggest that the therapeutic actions of these botanicals are not generally improved by extensive isolation of their individual constituents, and that the total therapeutic mechanism involved is quite complex, involving a substantial number of compounds in addition to the phenols, and piperidine compounds present. In this respect, isolation of individual constituents produce the undesirable effect of to some degree dismantling the full therapeutic action of the compound.

Sample F is the exception containing a purified isolate (capsaicin) of the primary pungent principal found in red pepper and other capsicums. Sample F also has perhaps 3 times the capsaicinoid, and 6 times the capsaicin content of the most pungent species of capsicum known to exist in nature. Yet across the board, Sample F falls short of the basic botanical extract Sample A even though it has 40 times the capsaicinoid concentration of Sample A.

While the above tests provide important insight into some of the therapeutic actions of the current invention, they are of course only partially indicative of the full antimicrobial action present, even as the earlier carrot juice agar tests failed to reveal any activity at all. The fuller antimicrobial activity of the compounds described above are of course observed in the actual treatment of disease, wherein the bodily immune responses are also perhaps modulated. These compounds repeatedly cure dermatophyte infections in as few as a single application. This cannot be said of Amphotericin B, or any of the other currently available prior art topical treatments.

The irritant acid amides found within both kinds of pepper, and their hydrolytes, appear to have direct fungicidal actions. Isodecylenic acid, one of the hydrolytes of capsaicin, may have antifungal properties superior to it's fatty acid chain relative, undecylenic acid, and offer important clues to the development of still other antimicrobials, structured similarly for increased effectiveness. Another hydrolyte of the capsaicinoids, 3-methoxy-4-hydroxybenzylamine (fig. 4), suggests a new class of amine antimicrobial compounds, derived from this, and other analogous structures.

OrganismMinimum Inhibitory Concentration

<u>test sample</u> (number of dilutions)				<u>standard</u> ug/ml
A	B	C	F	

Amphotericin B

<u>Candida Albicans</u> ATCC 10231	16	16	8	8	1.56
<u>Candida Albicans</u> 579a	16	16	8	8	1.56
<u>Candida Albicans</u> 442	16	16	16	16	1.56
<u>Candida Albicans</u> ATCC 38247	256	16	8	256	25.00
<u>Candida Albicans</u> ATCC 62376	16	16	8	8	1.56
<u>Candida tropicalis</u> NRRL-Y-112	16	32	16	16	1.56
<u>Candida kefyr</u> ATCC 28838	64	32	16	16	3.12
<u>Torulopsis glabrata</u> ATCC 15545	16	32	16	8	3.12
<u>Cryptococcus albidus</u> ATCC 34140	4	8	8	16	1.56
<u>Saccharomyces cerevisiae</u> GSI-36	16	16	8	16	1.56
<u>Aspergillus niger</u> ATCC 16404	16	4	4	4	1.56

Spec: Yeast extract Nitrate Broth + Glucose, water solvent, 48 hour Incubation, all Samples precipitate at 50% in YNB+G.

Sample A = cayenne pepper\* Sample B = black pepper\* Sample C = ginger\*  
Sample F = capsaicin (commercially pure 8-methyl-N-vanillyl-6-nonenamide)  
25mg/ml pure ethanol.

\*tincture 3:1 ground spice in ethanol 18 hours @ 22C.

Other possible antimicrobial agents found in pepper plants, that may play a role in producing curative results, are the phytoalexins such as the compound capsidiol, found in plants of the Solanaceae family which includes capsicums. A group of antimicrobial agents not normally present in the plant, phytoalexins are produced by the plant, only in response to trauma caused by heat, cold, mechanical injury, or attack by insects, or microbes. Capsidiol, and other of the phytoalexins produced by Solanaceae species, have antifungal properties against fungi that are pathogenic to the plant. While these fungi are not pathogenic to man, it is possible that capsidiol, or another phytoalexin produced in response to their challenge has antifungal action against fungi that are pathogenic to man, as well as those pathogenic to plants. It is therefore possible that capsidiol, or another phytoalexin may play a role in curing fungal disorders in man and animals, as well as plants.

Dehydration is another possible therapeutic action of pepper compounds. In the treatment of superficial mycoses, pepper extracts appear to dry the skin to a degree that may be inhospitable to fungi. Perhaps the result of increased permeability, or the formation of salts on the skin, the skin, though drier, is not uncomfortably so, and may have at least a fungistatic effect.

The prophylactic action of pepper extracts is another important therapeutic possibility. In addition to having apparent immediate fungicidal action in the treatment of superficial mycoses, pepper compounds also appear to remain in the skin for perhaps ten days after treatment, to prevent reinfection. Patients often report the reoccurrence of the warm, tingling sensation in treated areas while bathing, sometimes days after treatment. Exposure to water appears to also restimulate its therapeutic action as well. If feet, or skin become moist, and sweaty, the therapeutic action is intensified, at the same pathogenic fungi would normally proliferate. This provides a shield against reinfection due to recontamination, and protects the skin while it heals.

Pepper compounds also appear to function as a vulnerary, aiding, and accelerating the healing and regeneration of tissue. As tissue damage can be severe in certain forms of dermatophytosis, such as favus, nail infections, and athlete's foot, it becomes necessary to heal the damaged tissue before full cure is possible. Pathogenic fungi, finding opportunity in damaged skin for example, will often continue to reinfect those areas unless the skin is healed. This is perhaps one reason prior art medications are so ineffective towards cure. The skin is not allowed to heal quickly enough to safeguard against repeat

infection, as healthy, whole skin is the best protection against reinfection. The particularly high vitamin, and other nutrient content of capsicum for example, may have a further healing effect, as pepper compounds appear to stimulate the healing process of the skin, and encourage regeneration, growth, and normalization of function.

The high concentration of antioxidant compounds such as vitamin E, aromatic amines, phenols, and amino phenols found in pepper, particularly capsicum may also facilitate an antifungal effect beyond a generalized aid to healing. These antioxidants may interfere with the action of digestive enzymes secreted by the fungi, that are necessary for ingestion of nutrition; in effect starving the fungi.

Conversely, the very high concentration of vitamin C, a known oxidant, may also interfere with the ability of the fungi to digest, and ingest nutrition, by instead oxidizing it's food compounds before they can be absorbed.

It is also possible that high concentrations of citric acid, or vitamins found in pepper, are directly toxic to the fungi.

The observed keratolytic action may also have an antimicrobial effect, by perhaps interfering with the ability of pathogenic microorganisms such as fungi to digest, or ingest the keratin on which they feed.

Lastly, it will prove further helpful to witness the dramatic healing effect of pepper compounds in actual treatment of disease.

In a study of eight patients, all infected with various forms of dermatophytosis, complete cure is obtained after one topical application of the medication of the current invention in five of the eight cases studied. The other three cases studied are cured within half a dozen treatments or less. None of the patients are taking any kind of medication for ringworm, or for any other disorder, and no special sterilization measures of clothing, furniture or bedding are taken, beyond otherwise good personal hygiene.

In the first portion of the study, a family of three, all afflicted with ringworm, are completely healed after a single topical treatment with a pepper compound.

The infant has developed approximately six ringworm lesions about the back of the scalp, and back, and right side of the neck. The first few lesions were noticed a month before.



The mother of the infant has about six ringworm lesions on the right arm, most on the outside bicep. The appearance of the lesions was first noticed approximately three months before.

The father of the infant has approximately eight ringworm lesions on the left arm, most on the outside bicep. ~~The right arm~~ has four lesions, also on the outside of the bicep. Four other lesions appear on the shoulders, and lower back. The man first noticed lesions of this type approximately eight years earlier.

On all three subjects, the ringworm lesions have the same general appearance. The lesions are ring shaped, with slightly raised outer borders that are sometimes crusty. The lesions are red, with a smooth, and sometimes scaly interior. A clear, sticky fluid sometimes covers the lesion. The average diameter of the ring is about 15mm (.6"), with some as large as 20mm (.8"). The lesions appear, and remain for several weeks, sometimes disappearing, leaving lighter colored skin at the site of the prior lesion.

The man is first to be treated with a preparation of capsicum, wherein a **plaster** is applied to three lesions on the left bicep. A very slight, momentary tingling sensation is reported. The sensation lasts for about the first five minutes after application, and is not uncomfortable. The **plaster** is left on the skin for about one hour, then rinsed off with water. Afterward, the lesions appear redder than they did prior to application of **plaster**. After six hours, the lesions appear to be whiter, with the coloration being more similar to the skin tone of the healthy skin, than prior to treatment. At twenty hours, all three lesions appear healed, as it requires very close examination to reveal the site of the prior lesion. The characteristic patch of lighter colored skin that normally accompany lesions that have healed by themselves is not present.

The other dozen or so lesions found on the man are examined, and found to be substantially unchanged from their last examination the day before. Another examination on the third day yields the same results, with no sign of the three lesions that were treated and healed, and little change in the untreated lesions.

The other dozen ringworm lesions on the arms and trunk of the man, are treated with the same capsicum **plaster**, with identical results. All twelve lesions, regardless of location, are healed with the exact location of the prior lesion being difficult to determine because of the advanced degree of healing of the skin in that area.

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One week later, the woman is treated with the same capsicum **plaster** as the man, with similar results. At three days after treatment, all six lesions are completely healed in similar fashion to those on the man.

One week after the woman is treated, the infant girl is also treated with the capsicum **plaster** in the same manner as both her parents, and is healed in the same way, with the disappearance of all lesions within about one day. It is also interesting to note that the infant girl displays no sign of discomfort when the medication is applied, and does not cry, or even appear to take notice of the treatment.

Regular examinations of these three patients, over a period of several months, fails to identify the reappearance of one single ringworm lesion in any one of them. Each lesion of the patient is completely healed of ringworm, after just one single topical treatment with my medicine. 100% cure of twenty-eight lesions on three subjects is accomplished after a single dose of my medication, without reappearance of a single lesion. This is done without sterilization measures, and aside from any other medication whatever.

In another portion of the study, a woman in her middle thirties is healed of athlete's foot within hours of a single treatment of my medication. The woman works a full time job, in which she is required to be on her feet most of the time. Approximately one week after having purchased a more comfortable pair of shoes for work, the woman develops an inflammatory variety of athlete's foot. The primary symptoms are intense itching on top of the toes and foot, felt mostly in bed at night, along with a bad, musty foot odor. The itching is now interfering with sleep each night.

The woman soaks her feet in a bath, prepared from **infusion** of capsicum, for fifteen minutes. The woman reports a warm, tingling sensation that lasts about ten minutes. This treatment is administered at 8:00 p.m.. The woman retires for the evening at 10:00, and does not experience any of the itching characteristics of the previous evenings. For three weeks the woman reports not a single recurrence of the itching on the feet. She continues to wear the same footwear as before, and does not take any kind of sanitary, or other precautions to avoid reinfection.

After about three weeks, the woman begins to notice a gradual return of the itching on top of the feet that she had experienced before. Within another week or two, the itching is as intense as ever, and is again interfering with sleep.

The woman's feet are treated with a **lotion** of capsicum, using raw aloe vera gel as the lotion carrier. **Lotion** is applied to the feet, and rinsed off with water at the end of half an hour. The treatment is administered at 8:00 in the evening, before the woman retires for the evening at 10:00. The woman reports no itching that evening, nor afterwards, for many months. She disposes of the comfortable shoes, she had bought for work, and has no further recurrence of athlete's foot symptoms. The woman is completely healed of athlete's foot after just one single treatment with my medication!

The sixth case involves a five year old girl, who is completely healed of a recalcitrant case of dry athlete's foot. Prior to treatment, the child's feet are peeling severely in the areas between the toes, and on the entire sole of the foot. Loose skin, in pieces as large as about 4mm (1/8") square are hanging around the lower edge of the ball of the foot. The entire sole of the foot is callused, and has a wrinkled appearance.

Deep cuts occur periodically on the ball of the foot and around the base of the toes, particularly the great and small toes. The child often complains that her feet hurt from the cuts, but otherwise describes no other discomfort or symptoms. The girl has had these symptoms for about three years, since age two years.

At age two years, the girl develops a particular affection for a certain pair of shoes, and wears them constantly, refusing to wear other shoes. Weeks later, the girl develops a very offensive foot odor. Afterward, her feet gradually develop the symptoms described above, becoming chronic over the next three years.

An ethanol **tincture** of capsicum is applied to the girl's feet. The girl complains about a stinging sensation in the cuts around her great and small toes. The girl cries for about five or ten minutes, then reports that the sting is gone. The girl is also treated with the same capsicum **tincture** on days three and five, after the initial treatment. The investigator performs these second and third treatments because he is not sure if the first treatment is sufficient to penetrate such thick calluses on the soles of the feet, having never treated such badly damaged skin with this particular treatment.

On day three, just prior to the second treatment, the feet are examined and appear slightly improved. The cuts around the toes have formed scabs, and no discomfort is reported by the girl after application of the tincture.

On day five, the feet are again examined before receiving the third treatment, and again appear to be further improved. The cuts are continuing to scab over and heal, and the girl reports no discomfort from the medicine. This general trend continues for the next several days, yet treatment is not again administered.

By the fourteenth day, the feet are nearly, completely healed. There are no cuts or scabbed cuts, and no peeling or loose skin. The calluses are nearly, completely reduced, and the skin has a healthy color and texture, and no longer has a wrinkled, ragged appearance. It is not possible to determine that the girl has ever had athlete's foot, as her feet are healthy and normal. The child is excited that her feet are "like new again".

On day twenty one, the girl's feet are again examined. The skin around the bottom and sides of the toes has succumbed to reinfection, as the skin is again peeling, though not as severely as before the first treatment.

At six weeks, the girl's feet have returned to the pretreatment condition. The skin on the sole of the feet is thickened and callused. The skin on the soles and between the toes is peeling and has a ragged appearance. Cuts appear periodically at the base of the toes, on the heel and at the ball of the foot. The dry athlete's foot is back in full force.

The reinfection of the girl's feet is not presumed to be the result of recontamination, as no sanitary measures have been taken to prevent reinfection, and the girl continues to wear the same footwear as before the treatment. As these pathogenic fungi find opportunity in damaged skin tissue such as that described, the skin must be healed to prevent reinfection. The best protection from reinfection being healthy, undamaged skin.

This is one reason why the prior art has such difficulty curing this type of ringworm. The therapeutic action of prior art antifungals is so weak and slow acting, it arrests the resident fungi only enough to allow the healing process of the skin a slight advantage.

This is why a case of dry athlete's foot can easily require twelve weeks of daily, multiple treatments with prior art medications to provide cure, which is usually only temporary.

The dramatic improvement of the girl's feet between the last treatment on day five, and the examination on day fourteen suggests accelerated healing over any activity of fungi during this interval. It also

suggests a prophylactic action by my medicine that may provide protection for perhaps seven days or more.

Recalling complete cure after a single dose of my medicine in the first five cases leads to the conclusion that the fungi are eradicated on initial contact with my medication. What distinguishes them from this sixth case is the relatively minor degree of skin damage they suffered, in relation to the present case. This further supports the notion of the prophylactic action of my medicine, as seven days or less is ample time to heal the minor skin damage caused by the body ringworm lesions.

In an attempt to determine the maximum duration of capsicum's prophylactic effect, and to compare it's performance with that of synthetic capsaicin, the synthetic version of the primary irritant found within natural capsicum, the girl's feet are again treated.

Prior to treatment, the girl's feet have again returned to their original, recalcitrant condition that was noted prior to the first treatment. The girl's feet are peeling severely on the bottom and sides of the toes, and on the ball of the foot. The skin in this area is thickened, and callused, with deep cracks sometimes resulting in painful cuts. The skin has a wrinkled, dry, and ragged appearance, with intermittent red blotches, occupying about half the total surface area. Small cuts appear periodically around the base of the great and small toes, which often cause pain, especially when walking.

A **lotion** of capsicum, consisting of 4 cm<sup>3</sup> ( 4 teaspoon) of ground red pepper mixed with 48 cm<sup>3</sup> (12 teaspoons) of raw, aloe vera gel, is applied to the child's left foot. The girl describes a tickling sensation as **lotion** is being applied, and is laughing. About three minutes afterward, the girl begins crying, saying that the cuts on her toes are burning. She continues to cry for about ten more minutes, and afterward indicates that the burning has gone.

At the same time, an **ointment** of capsaicin, consisting of about .03 percent capsaicin (from oleoresin) in turpentine oil is applied to the right foot. There are no cuts on the right foot at this time, and the girl reports no discomfort from the medication.

The medications described above are applied once each week for the next two weeks, and observed regularly over the next three weeks, with little notable change the first few days.

On day three, the feet are examined, and appear to be showing signs of improvement. The peeling does not seem as severe, and the red

blotches look as if they are fading. The cuts on the left foot are healing, and show no sensitivity when firmly squeezed with the fingers.

On day four, the feet are again examined, and look much better than the previous day. The peeling is again reduced, and the red blotches have completely disappeared. ~~The right foot looks slightly better than the left,~~ suggesting the therapeutic effectiveness of the capsaicin ointment. The cuts on the left foot show further progress in healing.

Upon examination on the sixth day after treatment, the child's feet look very much improved. The loose skin has for the most part worn away, being replaced by healthy skin that shows no scaling, or discolor. The cuts on the left foot have disappeared, and both feet show reduced skin thickness, and only faint reminder of cracks that are mostly healed. Both feet look about the same, suggesting equivalent therapeutic performance between capsicum and capsaicin preparation.

The examination of day seven reveals little change in the condition of the feet from day six except that they appeared slightly better on day six. Small cuts along the base of the small toe on the right foot are not causing discomfort, as the medicine is applied for the second time.

Subsequent examinations of the next seven days reveal a similar pattern to that of the prior week. Little change is observed the first few days after treatment, with very noticeable improvement being observed between the fourth and sixth day after treatment. This pattern is also established on days eleven through thirteen, yet without substantial advance in the stage of healing beyond that observed on the sixth day.

It is evident that a single weekly application of my medicine produces substantial improvement in recalcitrant cases of athlete's foot. Though this improvement is sustained, it is not usually sufficient to induce full cure, at least within a three week span.

Nor does the degree of improvement compare to the results of the prior study, in which the medication was applied three times within the first week. Depending upon the case, two to four applications per week should be sufficient to provide complete, and sustained cure for recalcitrant cases of athlete's foot.

To demonstrate a complete cure for recalcitrant athlete's foot, and to compare the performance of a red pepper (*Capsicum frutescens*) extract with that of one made from black pepper (*Piper nigrum*), the girl's feet are again

treated. The girl's right foot is treated with an ethanol **tincture** of capsicum made from ground red pepper, while the left foot is at the same time treated with a similar **tincture** prepared instead with an equal amount of black pepper.

The girl's feet are treated eleven times, once every other day, over a period of three weeks. The pattern of previous tests is also observed in this trial, with both the red, and black pepper tinctures performing with equal effectiveness. As in the other tests with the girl, significant improvement is observed between the fourth, and sixth day after treatment, with dramatic improvement being noted at two weeks. At three weeks, very little sign of the prior disorder remains, and the condition does not return after weeks of observation. The girl is healed of recalcitrant athlete's foot, with just eleven topical treatments over a period of less than three weeks.

In the seventh case study, a woman of sixty is cured of a dry variety of athlete's foot. Prior to treatment, the woman's feet have peeling skin between the toes, and thickened soles with cuts on the underside of the heel.

The woman's feet are soaked in a capsicum **tea** for fifteen minutes at a time, once a day, for five days. On the second day, the woman complains that her feet are very dry, and that one of the cuts on her heel is making walking difficult because of the pain. By the fourth day, she indicates the cessation of those symptoms. After eight weeks, the feet are examined and the skin appears healthy, with no sign of peeling or thickening of the skin. The woman indicates that after the fourth day of treatment, she did notice the reemergence of symptoms at the time of the eight week examination, and felt cured since.

In the eighth case study, a boy of thirteen is completely healed of a severe fungal infection of the face, and neck after just two weeks of treatment with my medication.

Over a period of nearly five months, the boy has been suffering from what is described as an angry, bright red rash about the face, from beneath the eyes, down to the bottom, and sides of the neck. The boy's father describes the disorder as "literally eating his son's face away". The boy, and his family are for some time quite distressed, as treatment administered by a general practitioner, and two dermatologists over more than four months, fails to heal the condition. The expense of treatment is nearing \$1,000 out of pocket. The visits to the physician, have cost the parents more than twenty hours away from work, and the boy must be excused from school the same

amount of time. The boy is of course doubly distressed, as in addition to the discomfort of the disease, he must bear the humiliation of wearing this rash on his face that is more horrible in appearance than a severe case of acne.

A skin scraping sent to a laboratory reveals the presence of fungal hyphae, not of the ringworm variety.

The boy is given griseofulvin orally, but must discontinue treatment after one week as a result of severe nausea. The boy is then given tolinaftate topically, and has shown no significant improvement in the condition over a period of several weeks.

The boy is then given lotion prepared with capsicum, and instructed to apply the medication once every other day after bathing until symptoms disappear. All other treatments are also discontinued.

The boy's father administers the treatment as prescribed, and is seeing noticeable improvement by the third day. The condition continues to improve over this period, and by the tenth day the skin is almost completely healed, with barely a remnant of the prior disease remaining. To say the least, the boy's family and friends are amazed, and astounded at the rapidity of cure of this horribly unsightly condition, that had persisted for so many months before without improvement, often referring to the medicine as "a literal Godsend!"

The treatment is discontinued after only two weeks, and the boy is healed without relapse after many weeks of observation even until the time of this writing.

Thus the reader will see from these several examples that treatments containing pepper extracts provide a degree of effectiveness that is many generations ahead of the prior art. Single application cure of dermatophytosis, being unheard of among prior art treatments, is the usual result with the medication of my invention. No longer is it necessary for suffers to endure prescription therapies, which are slow acting, time consuming, expensive and potentially dangerous with many other unpleasant adverse effects. With my medication, embodied in the form of a topical, over the counter treatment, even recalcitrant cases of athlete's foot can be cured with a few periodic applications of my medicine. Instead of months of antibiotic therapy, administered by a dermatologist, the sufferer can cure the condition themselves, with a safe, inexpensive and astonishingly power medicine, such as mine.



While my above description includes many specificities, these should not be regarded as limitations on the invention, but rather as an exemplification of certain preferred embodiments.

Accordingly, the scope of the invention should not be determined by these illustrated embodiments, but by the appended claims, and their legal equivalents.

**Abstract**

A new class of general anti-fungal compounds extracted from pepper, ginger, and other plant species containing vanillyl (Fig. 3), and piperidine (Fig. 7) ring structures typical of the pungent principals found in pepper, and ginger. The role of these structures, their attached hydrocarbon groups, and other compounds found within the plant extract is demonstrated in the topical treatment of various superficial fungal infections.